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| 10/067,996 | 02/08/2002 | Ruiping Liu | MEMORY-2 | 9946 |

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|---|---|
| BERCH, MARK L | |

| ART UNIT | PAPER NUMBER |
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| 1624 | |

DATE MAILED: 12/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/067,996 | LIU ET AL. | |
| | Examiner | Art Unit | |
| | Mark L. Berch | 1624 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on 12/6/05.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-36,38-42,46-48,50,51,54,56,59-61,68 and 70-82* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-36,38-42,46-48,50,51,54,56,59-61,68,70-73 and 75-82* is/are rejected.

7)☒ Claim(s) *74* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

*Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 12/6/05 has been entered.

*Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 6, 10, 16-17, 21, 27-32 and 60-61, 68, 70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kelley(1990) i.e. Reference 4 of 11/6/2002 submission or Reference A34 of the 4/15/2002 IDS.

Compound 2 is an antiviral against rhinovirus type 1B. The species is excluded by proviso, but this methyl compound is a homolog of the corresponding ethyl compound, i.e. compound where R1 in the claims is ethyl. Compounds that differ only by the presence or absence of an extra methyl group or two are homologues. Homologues are of such close structural similarity that the disclosure of a compound renders *prima facie* obvious its

homologue. As was stated in *In re Grose*, 201 USPQ 57, 63, "The known structural relationship between adjacent homologues, for example, supplies a chemical theory upon which a prima facie case of obviousness of a compound may rest." The homologue is expected to be preparable by the same method and to have generally the same properties. This expectation is then deemed the motivation for preparing homologues. Of course, these presumptions are rebuttable by the showing of unexpected effects, but initially, the homologues are obvious even in the absence of a specific teaching to add or remove methyl groups. See *In re Wood*, 199 USPQ 137; *In re Hoke*, 195 USPQ 148; *In re Lohr*, 137 USPQ 548; *In re Magerlein*, 202 USPQ 473; *In re Wiechert*, 152 USPQ 249; *Ex parte Henkel*, 130 USPQ 474; *In re Jones*, 74 USPQ 152, 154; *Ex Parte Fischer* 96 USPQ 345; *In re Fauque*, 121 USPQ 425; *In re Druey*, 138 USPQ 39; *in re Bowers and Orr*, 149 USPQ 570. In all of these cases, the close structural similarity between two compounds differing by one or two methyl groups was itself sufficient show obviousness. Note also *In re Jones*, 21 USPQ2d 1942, which states at 1943 "Particular types or categories of structural similarity without more, have, in past cases, given rise to *prima facie* obviousness"; one of those listed is "adjacent homologues and structural isomers". Similar is *In re Schechter and LaForge*, 98 USPQ 144, 150, which states "a novel useful chemical compound which is homologous or isomeric with compounds of the prior art is unpatentable unless it possesses some unobvious or unexpected beneficial property not possessed by the prior art compounds." Note also *In re Deuel* 34 USPQ2d 1210, 1214 which states, "Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily

contemplate making them to try to obtain compounds with improved properties." See also MPEP 2144.09, second paragraph.

In addition, species 11, having the cyclopropyl and 9-methyl benzyl, is excluded by proviso, but it renders the corresponding compound having 9-ethyl benzyl as a homolog for the same reason. In addition, it renders obvious the position isomer, i.e. the meta-methyl benzyl or the ortho-methyl benzyl. It is well established that position isomers are prima facie structurally obvious even in the absence of a teaching to modify. The isomer is expected to be preparable by the same method and to have generally the same properties. This expectation is then deemed the motivation for preparing the position isomers. This circumstance has arisen many times. See: *Ex parte Englehardt,* 208 USPQ 343, 349; *In re Mehta,* 146 USPQ 284, 287; *In re Surrey,* 138 USPQ 67; *Ex Parte Ullyot,* 103 USPQ 185; *In re Norris,* 84 USPQ 459; *Ex Parte Naito,* 168 USPQ 437, 439; *Ex parte Allais,* 152 USPQ 66; *In re Wilder,* 166 USPQ 545, 548; *Ex parte Henkel,* 130 USPQ 474; *Ex parte Biel,* 124 USPQ 109; *In re Petrzilka,* 165 USPQ 327; *In re Crownse,* 150 USPQ 554; *In re Fouche,* 169 USPQ 431; *Ex parte Ruddy,* 121 USPQ 427; *In re Wiechert,* 152 USPQ 249, *In re Shetty,* 195 USPQ 753; *In re Jones,* 74 USPQ 152, 154. For example, "Position isomerism has been used as a tool to obtain new and useful drugs" (Englehardt) and "Position isomerism is a fact of close structural similarity" (Mehta, emphasis in the original). See also MPEP 2144.09, second paragraph.

Third, note species 8, 9, 12, 14, 15, 17, 18, 21 and 22. These all differ from claim 1 in that these have an extra methyl group on the amino N. Such a variation is considered obvious because of the close structural similarity. See *In re Hoeksema,* 154 USPQ 169; *Ex*

*parte Weston*, 121 USPQ 428; *Ex parte Bluestone*, 135 USPQ 199; *In re Doebel*, 174 USPQ 158.

Claims 1-3, 6, 10, 16-17, 21, 27-32, 35, 38-42, 46-48, 50-51, 54, 56-57, 59-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bourguignon i.e. Reference 5 of 11/6/2002 submission or Reference A37 of the 4/15/2002 IDS.

The compounds are PDE4 inhibitors, i.e. have the same utility as here. Accordingly, method claims are rejected as well.

Compound 6i corresponds to R2=benzyl, R1=H, and is excluded by proviso. However, it renders the corresponding homolog where R2= alpha, ortho or meta methyl-benzyl obvious, for reasons set forth above. It also renders obvious the chain homolog where R2 is phenethyl, i.e. $(CH_2)_2$-Phenyl rather than $(CH_2)_1$-Phenyl. It has long been established that this type of difference --- varying the size of a chain --- constitutes a form of homology, and is a fact of very close structural similarity, rendering the homolog obvious. See specifically *In re Shetty*, 195 USPQ 753; *In re Wilder*, 195 USPQ 426 and *Ex Parte Greshem*, 121 USPQ 422, all of which feature a compound with a $C_2$ link rejected over a compound with a $C_1$ link, precisely the situation here. Similarly, *In re Chupp*, 2 USPQ2d 1437 and *In re Coes*, 81 USPQ 369 have a compound with a $C_1$ link unpatentable over prior art showing $C_2$ link. Note also *In re Schaub*, 190 USPQ 324, 326, where compounds with $C_5$ and $C_6$ chains were called "adjacent homologs in the classic sense". *Ex parte Ruddy*, 121 USPQ 427 has a $C_3$ link unpatentable over a $C_1$ link. *Ex parte Nathan*, 121 USPQ 349 found the insertion of a $C_2H_4$ link obvious. In all of these cases, the variation was found to be obvious on the basis of close structural similarity; no secondary teaching was employed.

Compound 6d corresponds to R2= F-benzyl, R1=methyl, and is excluded by proviso. First, the corresponding R1=butyl derivative is obvious, because the reference teaches R1=butyl in the extremely similar 6a (both are 9 F-benzyl), so that the butyl is an obvious variation. Second the ethyl compound, i.e. R1=ethyl would be obvious as an adjacent homolog for reasons set forth above. Note that this is the second species in claims 35, 40 and 50.

The same is true for 6k, which corresponds to R2= 2-phenyl ethyl, R1=methyl, and 6l, which corresponds to R2= methyl, R1=methyl. In addition, 6l renders obvious the corresponding R2= ethyl, R1=methyl species as a homolog at the 9-position; n ote that such is not excluded by proviso.

Claims 1-2, 4, 27-29, and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kelley(1997) i.e. Reference A38 of the 4/15/2002 IDS.

The compounds are antipsychotic agents. Compound 80 (see table 7) corresponds to R1=cyclopropyl, R2= -($CH_2$)-cyclopropyl. This species is excluded by proviso g. However, it renders obvious the homolog compound where an extra methyl appears on the methylene, i.e. -($CHCH_3$))-cyclopropyl. Such a homolog compound is structurally obvious for reasons set forth above. In addition, the reference itself provides a motivation for this exact alteration. Table 6 deals with R1=cyclopropyl compounds, and this exact modification is shown. Note that compound 54 has the R2= -($CH_2$)-cyclopropyl and compound 60 has the -($CHCH_3$))-cyclopropyl. Compound 60 is twice as potent, which will motivate one of ordinary skill in the art to put the extra methyl on that exact position in compound 80, as this teaching arises specifically in the context of R1=cyclopropyl compounds. Hence, the R1=cyclopropyl, R2= -($CHCH_3$))-cyclopropyl is deemed obvious in view of the reference.

*Double Patenting*

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3, 6-36, 38-42, 46-48, 50-51, 54, 56-57, 59-61, 68, 70, 72-73, 80-82 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and others of copending Application No. 10636996. Although the conflicting claims are not identical, they are not patentably distinct from each other because there is no line of demarcation between the two cases. As noted in the prosecution of 10636996, the claims of 10636996 read on the

monomethylamino choice by means of 6-ethyl having the C of attachment turned into a N. Such species are seen in the rejected claims of this case.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 38-42, 46-48, 50-51, 54, 56-57, 59-61, 70, 72, 75-79 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 2-53, and 62-81 of copending Application No. 10845354. Although the conflicting claims are not identical, they are not patentably distinct from each other because there is no line of demarcation between the two cases. This is the daughter case to 10067996, drawn to the cognition utility that falls within these claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

*Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5, 16-29, 33-34, 38-42, 46-48, 50-51, 54, 56-57, 59-61, 68, 70-71, 80-82 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to

particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. The choice of "alkyl ether" for R2 is impossible. This is a molecule e.g. dimethylether, and hence has no valencies and cannot be a moiety.
2. The same is true for "hydroxamic acid, carboxamide" in the substituent list for aryl, heteroaryl and other places with aryl.
3. The choice of "oxo" is in error as a substituent on heteroaryl. Oxo as a substituent must replace 2 hydrogens, and a heteroaryl ring cannot have 2 hydrogens on a carbon.
4. The term "acyl" (as e.g. a substituent on aryl) is indefinite. Does this embrace acids of S? P? As? What does the stem look like, i.e. if the acyl is e.g. RC(O), what is R? In carboxylic acid acyls, does the carbon count include the carbon of the carbonyl?
5. The starting material for the claim 71 process makes no sense. It says that it starts with an adenine substituted on the 6-N with R1. But adenine does not have a 2-$CF_3$ group. Thus, one must either start with a starting material with such a group present, or one must add a step for that.
6. The reference to "PDE4" in claims 57 and 68 is unclear. The PDE4 family is encoded by four genes and thus there are actually 4 PDE4 types, PDE4A, PDE4B, PDE4C, and PDE4D, and theses can occur in splice variants as well. These generally arise from the presence or absence of two unique N-terminal domains called upstream conserved regions 1 and 2 (UCR1 and 2), and other pieces which may be present. UCR1 and UCR2 have been shown to form a module necessary for the activation of PDE4 upon phosphorylation by the cAMP-dependent kinase (PKA). For example, there are at least 5 different forms of PDE4B: PDE4B1, PDE4B2 (the short form), PDE4B3, PDE4B4 and

the very recently discovered PDE4B5. These various forms are not necessarily interchangeable. For example PDE4D is distributed mainly in certain inflammatory cells, while PDE4C is contained in brain cells. ERK MAP kinases phosphorylate and regulate the activity of PDE4B, PDE4C and PDE4D but not PDE4A isoforms. It is reduced PDE4D activity which apparently causes defective RyR2-channel function associated with heart failure and arrhythmias. In dendritic cells (the cells responsible for the priming of naive $T_h$ cells) it is predominantly PDE4A which is active, whereas monocytes mainly express PDE4B. It is the PDE4D5 isoform which preferentially interacts with the signalling scaffold proteins β-arrestin and RACK1. PDE4D3 likewise forms a signaling complex with AKAPs such as AKAP450.

7. The scope of claims 54, "disease involving decreased cAMP levels", and similar language in claim 68 is unknown. Claim 54 cover both diseases which cause, and are caused by, decreased levels of cAMP. cAMP is a ubiquitous second messenger that controls a wide range of cellular events including movement, growth, metabolism, contraction, and synaptic plasticity. It does this by activation of PKAs, a family of kinases, EPAC proteins, by regulation of VEGF-induced endothelial cell cycle protein expression and activation of other agents which are still being investigated. cAMP production is regulated by many other agents, including PGE2, SDF-1/CXCL12, Gpa1, Nitric oxide, Ca2+, Angiotensin II, Dopamine, adrenomedullin, Hemin, melatonin, Urotensin II, GLP-1, Forskolin, TSH, PACAP, EP3, PI3Kgamma and many other hormones, nutrients, etc., so that inhibiting PDE4 will not always have any effect on cAMP. There is simply no way of knowing what the scope of claims 54 and 68 are.

8. Similarly, there is no way of knowing what the scope of claim 68 is. There are dozens of inflammatory disorders as are discussed below, but which ones result from depressed cAMP or elevated PDE4 is unknown. There is no such list. The problem arises in part because PDE4 has such a wide range of effects. PDE4 as noted in the previous point, suppresses cAMP, and also norepinephrine. PDE4 regulates the L-type calcium current in human atrial myocytes, is involved in RyR2-channel function as noted above, is involved in chronic lymphocytic leukemia (CLL) apoptosis, regulates the signalling scaffold protein β-arrestin. PDE4 appears to be a component of the NMDA receptor-mediated signal transduction pathway.

Claims 38-42, 46-48, 50-51, 54, 56-57, 59-61, 68, 70, 72-73, 80-82 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444.
The analysis is as follows:

(1) Breadth of claims.

(a) Scope of the compounds. Owing to the broad scope of R1 and R2, millions of compounds are covered.

(b) Scope of the diseases covered.

I. For claim 54, as set forth above, it is entirely unclear which disease this would be, because there is only a limited understanding of the full role of cAMP in the body. Note that this claim language covers diseases caused by decreased cAMP, as well as disease which themselves cause decreased cAMP.

II. Claim 57 is taken to be embracive of the treatment of disease, in part because of the term "patient", and because the dependency of claim 47 indicates treatment of memory impairment. Indeed, as written, it covers any kind of patient at all; it is not actually limited to someone who needs their PDE4 levels suppressed. It thus covers the treatment of anyone who is a patient for any reason, even one having noting to do with PDE4.

III. Claim 47 covers any form of memory impairment. Memory is the capacity to retain and retrieve an impression of past experiences. Memory is thus inseparable from learning, as learning cannot take place without memory and memory is the expression of learning.

Memory can be classified in two ways. One is, approximately, by duration. The sensory memory (milliseconds to seconds) corresponds to the initial moment that an item is perceived by the sense. Some of this information in the sensory area is transferred to short-term memory (retention for seconds to minutes). The capacity of these memories is quite limited. Some of this information is consolidated into long-term memory (retention for days up to a lifetime). The capacity of long term memory is immense. There is also something called working memory, which refers to a short-term storage needed for certain mental

tasks but is not specifically defined in terms of duration, but rather in terms of purpose. It appears to be a form of short-term memory combined with some attentional control.

In addition, long term memory (the most important type) can be classified according to the information type. The two main categories are declarative (explicit) and non-declarative (implicit) memories. Declarative memory requires conscious recall, in that some conscious process must explicitly call back the information. This includes semantic memory, which concerns facts taken independent of context (mostly, general knowledge about the world); and episodic memory, which concerns information specific to a particular context, such as a time and place (mostly, personal memories and personal associations of a particular place or time, sometimes called autobiographical memory). The other main category's most important type is called procedural memory and is not based on the deliberate recall of information, but on an implicit learning of certain patterns about the world. This form of learning is responsible for improvements in performance due purely to repetition. Examples of this include Classical conditioning and motor learning (e.g. "muscle memory"), and many types of skills. The other type of non-declarative memory is perceptual-representational, a kind of "priming", so that the experience of an object on one occasion facilitates the perception of the same (or a similar) object on a later occasion.

Memory involves many different parts of the CNS, including basal ganglia, amygdala, the neostriatum, the cerebellum, the mammillary bodies and hippocampus.

The formation of memory requires three steps or stages: 1) Encoding (sensory registration, the processing of received information, including combination if the information comes from e.g. more than one sense organ), 2) Storage (creation of a permanent record of this encoded information), and 3) Retrieval (calling back this stored

information in response to some cue for its use). As all of these are essential; a dysfunction of any stage will result in memory impairment. Thus, if the intial encoding does not take place, or if this information is not transferred to short term memory, such as occurs in the various agnosias, then memory impairment will occur. If information cannot be moved from short term to long term memory (a process called anterograde amnesia), then memory impairment occurs. If retrieval from long term memory is delayed, if it cannot be performed (memories lost), or if it is defective (false memories), then there is memory impairment.

As a result of the wide range of different types of memories which the brain forms, and the great complexity of the processes for memory, this covers a very wide range of disorders.

These include language memory disorders, such as aphasias (e.g. conduction aphasia), apraxia, dysarthria, alexia, receptive dysphasia, and agraphia.

It includes many types of disorders called amnesias. There is anterograde amnesia (new events are not transferred to long-term memory) and retrograde amnesia (inability to recall events that occurred before the onset of amnesia). There is lacunar amnesia (loss of memory about one specific event), Fugue amnesia (Psychogenic amnesia or hysterical amnesia, including "repressed memories"), Childhood amnesia (inability to remember events from early childhood), Transient Global Amnesia (total memory loss), those arising from complex partial seizures, and alcoholic blackouts.

It also includes various agnosias, such as Prosopagnosia, Integrative agnosias, asogmatoagnosia, Associative agnosias, Time Agnosia, Apperceptive agnosia, object agnosia, finger agnosia, phonagnosia, central achromatopsia, topographical agnosia,

dyslexia, dyscalculia, right-left disorientation, Optic ataxia and Ocular apraxia, Color Agnosia, Simultanagnosia, Anosognosia, Auditory Agnosia (including amusia and word meaning deafness), and Somatosensory Agnosia (including Microsomatagnosia, Macrosomatagnosia, tactile agnosias and astereoagnosia), and constructional dyspraxia. There is also Korsakoff's syndrome (Memory loss caused by alcoholism) and Post-traumatic stress disorder (spontaneous, vivid retrieval of unwanted traumatic memories), and various types of false memory syndromes. There is the very common AAMI (age-associated memory impairment). Certain forms of Confusional States (e.g. those arising from Iatrogenic toxicity from some sedatives) will present acute memory disorders.

IV. Claim 68 covers inflammatory diseases which arise from decreased cAMP levels or elevated PDE4 levels or both. (It also covers allergic disease, but these are completely subsumed under inflammatory disease). As indicated above, there is no way of knowing which inflammatory diseases this does and does not cover, especially since PDE4 regulates, directly or via cAMP and various pro-inflammatory cytokines, so many different inflammatory practices. The analysis below assumes that it covers all.

Inflammation is the reaction of vascularized tissue to local injury; it is the name given to the stereotyped ways tissues respond to noxious stimuli. These occur in two fundamentally different types. Acute inflammation is the response to recent or continuing injury. The principal features are dilatation and leaking of vessels, and recruitment of circulating neutrophils. Chronic inflammation or "late-phase inflammation" is a response to prolonged problems, orchestrated by T-helper lymphocytes. It may feature recruitment and activation of T- and B-lymphocytes, macrophages, eosinophils, and/or fibroblasts. The

hallmark of chronic inflammation is infiltration of tissue with mononuclear inflammatory cells. Mechanistically, chronic
inflammation encompasses a broad spectrum of immunologic processes, including antibody formation, antibody-dependent cell-mediated cytotoxicity, and cell-mediated immunity (delayed-type hypersensitivity). Granulomas are seen in certain chronic inflammation situations. They are clusters of macrophages which have stuck tightly together, typically to wall something off. Granulomas can form with foreign bodies such as aspirated food, toxocara, silicone injections, and splinters.

Otitis media is an inflammation of the lining of the middle ear and is commonly caused by Streptococcus pneumoniae and Haemophilus influenzae.

Cystitis is any inflammation of the bladder, often caused by bacteria. Two ordinary types are eosinophilic and tuberculous cystitis. Interstitial cystitis (IC) is a particularly severe form, an inflammation of the bladder wall which may include Glomerulations. The origins and mechanism are largely unknown, and it isn't even clear whether there is just one form of the disease or several. There is no actual pharmaceutical treatment for the disease itself, although a few drugs can give some relief of symptoms, specifically Elmiron and DMSO.

Blepharitis is a chronic inflammation of the eyelids that is caused by a staphylococcus. Dacryocystitis is inflammation of the tear sac, and usually occurs after a long-term obstruction of the nasolacrimal duct and is caused by staphylococci or streptococci. Preseptal cellulitis is inflammation of the tissues around the eye, and Orbital cellulitis is an inflammatory process involving the layer of tissue that separates the eye

itself from the eyelid. These life-threatening infections usually arise from staphylococcus. Hence, these types of inflammations are treated with antibiotics.

There is also a wide assortment of forms of conjunctivitis, including seasonal allergic conjunctivitis, perennial allergic conjunctivitis, giant papillary conjunctivitis (GPC) (a chronic yet poorly condition associated with contact lens wear), Vernal keratoconjunctivitis and atopic keratoconjunctivitis. In addition to types of allergic conjunctivitis there is also bacterial conjunctivitis (e.g. from Streptococcus pneumoniae, Haemophilus influenzae, and Staphylococcus aureus) and viral conjunctivitis (e.g. from gonorrhea, herpes simplex, chlamydia, adenoviruses or enteroviruses) Parasitic conjunctivitis (e.g. from *Onchocerca volvulus, Loa loa, Wuchereria bancrofti* or *Trichinella spiralis),* fungal conjunctivitis (e.g. from *Candida albicans* or *Sporothrix schenckii),* Phlyctenular Conjunctivitis, Inclusion Conjunctivitis, immunologic conjunctivitis, irritant conjunctivitis (e.g. from burns, chlorine or air pollutants ), Radiation conjunctivitis, and assorted forms of neonatal conjunctivitis (which can be caused by e.g. a blocked tear duct).

Cholecystitis is gallbladder inflammation usually caused by a gallstone that cannot pass through the cystic duct. In those cases, it normally cannot be treated by pharmaceuticals but instead the gallbladder is removed. Cholecystitis without the formation of gallstones, called acalculous cholecystitis, is caused by bacteria such as Salmonella, Staphylococcus, Streptococcus (as part of scarlet fever), and leptospirosis, and thus may be treatable by treating the underlying infectious agent. Acute inflammation of the gall bladder can also arise from typhoid; treatment is with antibiotics.

The term "arthritis" is used for any kind of inflammation of the joints arising from a wide diversity of causes and mediators, many of which are unknown. It mostly commonly

refers to any of osteoarthritis, gouty arthritis, or rheumatoid arthritis. These are three totally different and unrelated disorders, which all have "arthritis" in their name and involve inflammation of the joints. Rheumatoid arthritis is an inflammatory disorder causing destruction of articular cartilage, in which macrophages accumulate in the rheumatoid synovial membrane. Mediators are cytokines, including IL-1, IL-18, TNF-I and IFN-K. It is thus an autoimmune condition where the body's immune system attacks its joints. In gouty arthritis, joint inflammation is caused by the formation of monosodium urate monohydrate (MSU) crystals within the joint space. Acute attacks of gout are treated with colchicine (to inhibit of MSU-induced chemotactic factor release by PMNs) and after the acute phase with allopurinol to control the blood levels of uric acid. Osteoarthritis is a degenerative cartilage disorder; cartilage breakdown causes bones to rub against each other. Causes include injuries, diseases such as Paget's disease, and long term obesity, but often the cause is unknown, and the full mechanism has not been discovered. It is treated with NSAIDs and COX-2 inhibitors. Complicating matters further is that fibromyalgia is sometimes also intended to be included in the loose term "arthritis". There is also Psoriatic Arthritis (including DIP, and spondylitis) which is believed to be autoimmune in origin but is a separate disorder from RA. There are also an assortment of infectious arthritis, i.e. arthritis caused by bacteria, rickettsiae, mycoplasmas, viruses (or vaccinations given to prevent viral infections), fungi, or parasites. Included in this category are various types of septic arthritis and mycotic arthritis, and viral arthritis, such as rubella arthritis, Lyme arthritis, Mumps arthritis, arboviral arthritis, syphilitic arthritis, parvovirus arthritis, tuberculous arthritis, Varicella arthritis, gonococcal arthritis, rubella arthritis, Reiter's syndrome (which includes a form of arthritis commonly arising from infection by

Chlamydia trachomatis) etc. These assorted disorders can arise from quite varied sources. Thus, in addition to the above, CPDD, sometimes called pseudoosteoarthritis, or pseudogout, arises from Calcium Pyrophosphate Deposition. It is treated with nonsteroidal anti-inflammatory drugs , corticosteroids and Colchicine. Menopausal arthritis is due to ovarian hormonal deficiency. Neuropathic arthritis (which comes in several forms, such as Charcot's disease) can arise from sources as diverse as Diabetes Mellitus, Steroid treatment, Leprosy, Chronic alcoholism, Heavy metal poisoning and Neoplastic peripheral neuropathy. Arthritis can also arise from injury to the supporting ligaments or other structures contained within or associated with the joint, a condition often called post-traumatic arthritis.

Sinusitis is the inflammation of the mucosal lining of one or more of the 4 cavities near the nasal passages (ethmoid, maxillary, frontal, and sphenoid sinuses). It commonly accompanies upper respiratory viral infections which obstruct the opening, but such obstruction can also arise from abnormalities in the structure of the nose, enlarged adenoids, diving/swimming, infections from a tooth, trauma to the nose, and foreign objects that are stuck in the nose. Bacteria, notably Streptococcus pneumonia, Haemophilus influenza, and Moraxella catarrhalis grown in the trapped secretions. In most cases it requires no treatment, but antibiotics may be given, along with acetaminophen for pain and nosedrops, for relief of symptoms.

Pharyngitis is infection and inflammation of the throat (including the nasopharynx, uvula, and soft palate)and tonsillitis is of the tonsils. These are caused by a variety of viruses (adenoviruses, influenza viruses, parainfluenza viruses, Epstein-Barr virus, enteroviruses, Herpes simplex virus), mycoplasmas (e.g. Mycoplasma pneumoniae), and

bacteria (Group A Beta Hemolytic Streptococci (GABHS), Streptococcus pyogenes, Neisseria Gonorrhea, Hemophilus Influenza Type B) as well as fungal infections, parasitic infections, cigarette smoke, and unknown causes.

Similarly, Osteomyelitis is the inflammation of bones, generally caused by bacteria (most commonly Staphylococcus Aureus). The disease can be caused by fungi or viruses. Dacryoadenitis, an inflammation of the tear gland, can arise from infectious mononucleosis, mumps, gonorrhea, or influenza.

Pneumonia is an inflammation of the lungs. Lobar pneumonia affects one or more sections (lobes) of the lungs. Bronchial pneumonia (or bronchopneumonia) affects patches throughout both lungs. Bacterial pneumonia is caused by various bacteria notably Streptococcus pneumoniae. Viral pneumonia is caused by viruses (such as respiratory syncytial, parainfluenza, and influenza), Other causes are fungi, mycoplasmas, rickettsias (especially Q fever), Chlamydia, or parasites. It can also occur as a hypersensitivity, or allergic response, to agents such as mold, humidifiers, and animal excreta, and in such a case would be treated with anti-allergic agents. Treatment may include antibiotics for bacterial pneumonia. Antibiotics may also speed recovery from mycoplasma pneumonia and some special cases. There is no clearly effective treatment for viral pneumonia.

Adult (or Acute) Respiratory Distress Syndrome (ARDS) is severe inflammation in both lungs resulting in an inability of the lungs to function properly. ARDS is a devastating, often fatal, inflammatory lung condition that usually occurs in conjunction with catastrophic medical conditions, such as pneumonia, shock, sepsis, and trauma. No specific therapies currently exist for ARDS patients. Treatment primarily involves

supportive care in an intensive care unit , including use of a mechanical ventilator and supplemental oxygen to help patients breathe.

Chronic bronchitis is a long-term inflammation of the bronchi, which results in increased production of mucus, as well as other changes. Chronic bronchitis has no specific organism recognized as the cause of the disease. Cigarette smoking is cited as the most common contributor to chronic bronchitis, followed by bacterial or viral infections and environmental pollution. Treatment is purely supportive and may include bronchodilators for inhaled medications, oxygen supplementation, lung reduction surgery and lung transplantation.

Chronic Obstructive Pulmonary Disease (COPD) is a slowly progressive disease of the airways that is characterized by a gradual loss of lung function. COPD includes chronic obstructive Bronchitis (which involves inflammation and eventual scarring of the bronchi) and emphysema (enlargement and destruction of the alveoli). Emphysema comes in several forms, including Congenital Lobar Emphysema, Bullous Emphysema, Centrilobular Emphysema (Proximal acinar emphysema), Panacinar (panlobular), Distal acinar (paraseptal) as well as Alpha-1 antitrypsin (AAT) deficiency, which is the genetic form of emphysema; patients often have both a form of bronchitis and emphysema. Ordinary chronic bronchitis is sometimes included with COPD even if there is no actual obstruction, and asthmatic bronchitis is generally included in COPD as well. Persons with COPD typically develop smaller air passageways, which can become clogged with mucus and have partially destroyed alveoli. There is no pharmaceutical treatment for COPD per se. Instead, treatment is supportive and designed to relieve symptoms and improve quality of life. Thus, oxygen is often given to partially compensate for the loss of lung function.

Bronchodilators can expand passageways in the lungs, Corticosteroids can reduce inflammation and Antibiotics can ward off bacterial infections, but none of these treat the COPD itself.

Acute bronchitis is the inflammation of mucous membranes of the bronchial tubes and is usually caused by infectious agents such as bacteria or viruses. It may also be caused by physical or chemical agents -- dusts, allergens, strong fumes -- and those from chemical cleaning compounds, or tobacco smoke. (Acute asthmatic bronchitis may happen as the result of an asthma attack, or it may be the cause of an asthma attack.) Acute bronchitis is usually a mild, and self-limiting condition, with complete healing and return to function. Most of the treatment is supportive of the symptoms, and may include analgesics, such as acetaminophen for fever and discomfort.

Asthma is a chronic, inflammatory lung disease involving recurrent breathing problems. It is characterized by three airway problems: obstruction, inflammation, and hyper-responsiveness. These lead to contraction of airway muscles, mucus production, and swelling in the airways. There are many different asthma triggers.

Myocarditis is an inflammation of the muscular middle layer of the heart (myocardium) Viruses, bacteria, and noninfectious diseases can cause it. Treatment is primarily supportive e.g. drugs may be used to improve the heart's ability to contract and to remove extra fluids from the body. Unless the underlying infectious agent itself is treatable, this inflammation is not itself treated.

Glossitis is inflammation of the tongue. Local causes of glossitis include bacterial or viral infection, mechanical irritation or injury from burns, rough edges of teeth or dental and oral appliances, or other trauma; exposure to irritants (tobacco, alcohol, hot foods, or

spices), and sensitization (to e.g. toothpaste, mouthwash, breath fresheners, dyes in candy, plastic in dentures or retainers) anemia and other B vitamin deficiencies, erythema multiform, pemphigus vulgaris, syphilis, and other disorders. It can be inherited. Corticosteroids such as prednisone may be given to reduce the inflammation. Antibiotics, antifungal medications, or other antimicrobials may be prescribed if the cause of glossitis is an infection. Anemia and nutritional deficiencies must be treated, often by dietary changes or other supplements.

Meningitis is the inflammation of the meninges—the surrounding 3-layered membranes of the brain and spinal cord, and the fluid it is bathed in, (CSF). It can be caused by virtually any known infectious agent. Thus, if it is caused by Haemophilus influenzae or Neisseria meningitis, the antibiotic derivative rifampin would be used.

Myelitis is inflammation of the spinal cord.

Dactylitis is an inflammatory affection of the fingers.

Inclusion body myositis in an inflammatory slowly progressive proximal myopathy which may cause dysphagia and mild to moderate muscle wasting. Steroids and immunosuppression have generally been generally ineffective. Its pathogenesis is unknown, but ubiquitin, prion protein, and tau protein has been found in these inclusions.

Encephalitis is inflammation of the brain itself, often caused by a group of arboviruses. Treatment of encephalitis is largely supportive because no specific antiviral agents, except for that which works against herpes simplex virus, are available for therapy.

Inflammation in the brain is a significant component of some important neurodegenerative conditions, including Alzheimer's Disease, AIDS dementia, Pick's Disease, Parkinson's Disease, and Huntington's Disease. The circumstances here are poorly

understood because while there does not appear to be lympho-infiltrative processes, there is neuropathological evidence for immune activation. Thus, inflammation may be a disease-aggravating or even a disease-ameliorating factor in pathogenesis, or a non-contributory consequence of the injurious cascade of neurodegeneration and thus incidental.

Hepatitis is an inflammation of the liver, usually caused by viral invasion, notably hepatitis A, B and C, but sometimes Epstein-Barr virus; herpes simplex viruses; measles, mumps, and chicken pox viruses; and cytomegaloviruses. Treatment, when possible, is with antivirals. Inflammation of the liver also take the form of alcoholic hepatitis. Lupoid hepatitis is an autoimmune disorder.

Hemorrhoids is an enlarged or varicose condition of the hemorrhoidal veins and tissues around the anus, either internal or external. Anything which obstructs the free circulation of the blood in the portal system will give rise to hemorrhoids. Constipation, straining at stool, diarrhea, dysentery, rough toilet paper, uncleanliness, pelvic tumors, displacement of the uterus and pregnancy are among the most common causes.

There is a series of inflammatory problems directly connected to neutrophil-endothelial cell adhesion (NECA). These include frostbite injury, bacterial meningitis, acute airway inflammation, allograft rejection, hemorrhagic shock, septic shock, ischemia and reperfusion injuries.

Urethritis is an inflammation of the duct that leads from the bladder to the body's exterior. It is often due to fecal contamination or irritation due to physical or chemical substances (e.g. introduction of foreign bodies into the urethra, bubble bath, or soap) or gonorrhea. Treatment may simply involve the withdrawal of the offending chemical agent, or the administration of antibiotics, when Neisseria gonorrhoeae is involved.

Inflammation can arise from the eruption of teeth in a child (teething).

Inflammation of the nails can arise from chronic paronychia, fungus (especially Candida albicans), trauma, impaired circulation, and dermatitis.

Bright's disease (or glomerulonephritis) is inflammation of the glomeruli and the nephrons, the structures in the kidney that produce urine. It usually results from an infection, such as a streptococcal infection, that occurs somewhere else in the body. There is no real treatment beyond relief of the symptoms.

Thyroiditis is an inflammation of the thyroid gland, and takes three forms. Hashimoto's Thyroiditis (chronic lymphocytic thyroiditis) is the most common type of thyroiditis. It is an autoimmune disorder, and treatment is to start thyroid hormone replacement. For De Quervain's Thyroiditis (subacute or granulomatous thyroiditis), treatment is usually bed rest and aspirin to reduce inflammation. Occasionally cortisone and thyroid hormone may be used. Silent Thyroiditis usually arises following pregnancy. Treatment is usually bed rest with beta blockers.

Regional enteritis (Crohn's disease or ileitis) is an autoimmune disorder which is associated with the presence of Mycobacterium paratuberculosis. It can affect any part of the gastrointestinal tract but most commonly affects the ileum. The inflammation is controlled primarily by regulation of diet, antibiotics if abscesses and fistulas are present, sometimes Prednisone and other corticosteroids, and surgery.

Another category of inflammatory disorders is Interstitial lung disease, or ILD, (interstitial pulmonary fibrosis), a term that includes more than 180 chronic lung disorders, which may be chronic, nonmalignant (non-cancerous) and noninfectious. Interstitial lung diseases are named after the tissue between the air sacs of the lungs called the interstitium

-- the tissue affected by fibrosis (scarring). The common link between the many forms of ILD is that they all begin with an inflammation. The three main kinds are bronchiolitis - inflammation that involves the bronchioles (small airways); alveolitis - inflammation that involves the alveoli (air sacs); and vasculitis - inflammation that involves the small blood vessels (capillaries). More than 80 percent of interstitial lung diseases are diagnosed as pneumoconiosis, a drug-induced disease, or hypersensitivity pneumonitis. Some other types are idiopathic pulmonary fibrosis, bronchiolitis obliterans, histiocytosis X, chronic eosinophilic pneumonia, granulomatous vasculitis, Goodpasture's syndrome and pulmonary alveolar proteinosis. The cause of interstitial lung disease is not known, however, a major contributing factor is thought to be inhaling environmental pollutants. Other contributing factors include Sarcoidosis, certain drugs, radiation, connective tissue or collagen diseases and family history. Treatments may include corticosteroids, influenza or pneumococcal pneumonia vaccine but these are of limited effectiveness.

Many Occupational Lung Diseases are inflammatory in origin, arising from repeated and long-term exposure to certain irritants on the job. These include for example asbestosis, coal worker's pneumoconiosis (caused by inhaling coal dust), silicosis (caused by inhaling free crystalline silica), byssinosis (caused by dust from hemp, flax, and cotton processing, also known as brown lung disease), aluminosis, anthracosis ("collier's lung", from the accumulation of carbon from inhaled smoke or coal dust in the lungs), chalicosis (stone-cutters' lung disease, due to inhaling stone dust), siderosis (occurring in iron workers, produced by the inhalation of particles of iron), tabacosis, hypersensitivity pneumonitis (caused by the inhalation of fungus spores from moldy hay, bird droppings,

and other organic dusts and occupational asthma (caused by inhaling certain irritants in the workplace, such as dusts, gases, fumes, and vapors).

Proctitis is a form of inflammation of the rectum, and includes Antibiotic-Induced Proctitis, Gonorrheal Proctitis, Herpetic Proctitis, Ischemic Proctitis, Radiation Proctitis, Syphilitic Proctitis and idiopathic proctitis.

Pulmonary Sarcoidosis causes small lumps, or granulomas, which generally heal and disappear on their own. However, for those granulomas that do not heal, the tissue can remain inflamed and become scarred, or fibrotic. Pulmonary sarcoidosis can develop into pulmonary fibrosis. Bronchiectasis, a lung disease in which pockets form in the air tubes of the lung and become sites for infection, can also occur. Treatment may include the use of corticosteroids.

Stomatitis, inflammation of the mouth, and mucositis, inflammation of the mucosa can arise from sources as diverse as Candida albicans, dentures, chemotherapy and radiation therapy to the head, neck or mouth ("Radiation mucositis"). It may be secondary to infection, trauma, systemic diseases or autoimmune mechanisms. These come in many forms, such as aphthous ulcers, Acute Necrotizing Ulcerative Gingivitis i.e. "trench mouth", and Lichen Planus. Herpetiform ulcers treatment has ranged from antibiotics, immunosuppressants and yogurt, to Lactobacillus capsules, tetracycline and systemic steroids. Palliative measures include topical anesthetics, Vitamin E, analgesics, and coating agents. Antiviral agents may be used if viral origin is established.

Rhinitis is a reaction that occurs in the eyes, nose and throat when airborne irritants (allergens) trigger the release of histamine. Histamine causes inflammation and fluid production in the fragile linings of nasal passages, sinuses, and eyelids. The two

categories of rhinitis are allergic rhinitis (seasonal and perennial) and nonallergic Rhinitis (including eosinophilic, rhinitis medicamentosa, vasomotor Rhinitis, neutrophilic rhinosinusitis, and others), which come from fumes, odors, temperature or atmospheric changes, smoke, etc. Treatments for nonallergic rhinitis include oral medications, inhaled medications, immunotherapy, and surgery for some conditions. Wegener's Granulomatosis is a disease that usually begins as a localized granulomatous inflammation of upper or lower respiratory tract mucosa and may progress into generalized necrotizing granulomatous vasculitis and glomerulonephritis. The cause is unknown. Although the disease resembles an infectious process, no causative agent has been isolated. Treatment is with immunosuppressive cytotoxic drugs.

Pancreatitis is inflammation of the pancreas and can arise from abdominal trauma, or the formation of gallstones that obstruct the common bile duct. It can be associated with excessive ingestion of alcohol; with disorders such as cystic fibrosis or Reye's syndrome; or with scorpion stings. Infectious causes include mycoplasmas, Epstein-Barr viruses, Coxsackie viruses, leptospirosis, hepatitis viruses, mumps, congenital German measles, Ascaris worms, and syphilis. The inflammation per se is generally not treatable. Treatment is usually supportive and consists of the management of pain and intravenous feeding.

Neuroretinitis is a type of inflammation of the retina and optic nerve of the eye ("optic neuritis"). It is often idiopathic. It frequently arises secondary to some kind of infection, such as Hepatitis B, HSV, EBV, influenza A, mumps, Coxsackie B, TB, salmonella, Lyme disease, syphilis, leptospirosis, Histoplasmosis, Toxoplasmosis, toxocara, Sarcoidosis and cat-scratch disease. Treatment is thus to the underlying cause. For example, Diffuse unilateral subacute neuroretinitis (DUSN) arises from nematodes deep in

the retina or in the subretinal space. Anthelminthic treatment is then used. When the origin is Toxoplasmosis, then anti-Toxoplasma medications such as Pyrimethamine. Vogt-Koyanagi-Harada syndrome (Harada's disease) is an acute inflammatory, immune-mediated disorder that can cause choroidal neovascularization, severe chorioretinal atrophy, and secondary glaucoma.

River blindness arises from inflammation of the eye caused by larvae (microfilaria) of the nematode *Onchocerca volvulus*, although the *Wolbachia* bacteria may be involved as well.

Other eye inflammations include scleritis and episcleritis, inflammation of tissues on the sclera; choroiditis, inflammation of the middle coat (choroid) of the eyeball, and uveitis, which is inflammation of the parts of the eyes that make up the iris.

Gastritis is inflammation to the stomach lining. Atrophic gastritis is characterized by the loss of the stomach cells that are responsible for manufacturing acid, pepsin, and intrinsic factor. This condition occurs in older people or those suffering from Helicobacter pylori. Erosive (hemorrhagic) gastritis occurs when shallow ulcers or sores develop on the upper layer of the stomach lining, usually because of the excessive ingestion of a stomach irritant such as aspirin or alcohol.

There can also be mentioned appendicitis, which can occur when a hard piece of stool blocks the opening of the appendix, causing swelling and inflammation.

The great majority of skin problems involve some type of inflammation, such as response to physical injury (e.g. sunburn, ticks, abrasion, or a bee string), acute allergic contact dermatitis (such as poison ivy), and infections (such as boils and cold sores). Ingrowing hairs, or pili incarnati, can cause acute pustular reactions. Cancerous lesions of

the skin frequently show some degree of inflammatory response. Acne's inflammation is caused by leakage of sebum and keratin debris outside the distended pilosebaceous duct. The bacillus Propionibacterium acnes, which populates the lesions, may also contribute indirectly to this inflammation by metabolizing the sebum to produce irritant fatty acids. Inflammation in skin problems is usually the result of the release of chemical mediators in the skin, notably histamine, peptides (kinins) and fatty acids (prostaglandins and leukotrienes), which are formed enzymatically in response to e.g. injury. Medications designed to counteract inflammation in the skin may or may not antagonize the effects of the particular type of mediator involved, if that is known. The inflammation can take many different forms, including redness, (from dilation of blood vessels); heat, (from increased blood flow); swelling (from leakage of fluid from the small blood vessels); whealing reactions (hives, nettle rash, urticaria) in which vascular changes predominate, and pain or itching. Blisters (from enzymes released from inflammatory cells, resident cells of the skin, or blood plasma components) can cause the breakdown of proteins responsible for the structural integrity of the skin, leading to serious inflammatory disorders such as pemphigus. In addition, the affected skin may feel indurated (hardened) because of the deposition of the coagulation protein fibrin and the infiltration by inflammatory blood cells (lymphocytes, histiocytes, and polymorphonuclear leukocytes).

Prostatitis, inflammation of the prostate, comes in several different forms, including those of bacterial origins, and those which are not, including chronic abacterial prostatitis and asymptomatic inflammatory prostatitis. Certain types of anti-inflammatory agents, such as non-steroidal anti-inflammatory medications (Ibuprofen and naproxen) along with muscle relaxants can be used in the non-bacterial cases.

There are a number of different forms of vasculitis, including Churg-Strauss vasculitis, consecutive vasculitis, granulomatous vasculitis of central nervous system, hypersensitivity vasculitis, (called also allergic or leukocytoclastic vasculitis or leukocytoclastic angiitis which arises from hypersensitivity to an antigenic stimulus), hypocomplementemic vasculitis, isolated vasculitis of central nervous system, nodular vasculitis, overlap vasculitis (polyangiitis overlap syndrome), pulmonary vasculitis including Wegener's granulomatosis, rheumatoid vasculitis, segmented hyalinizing vasculitis (livedo vasculitis), Polyarteritis nodosa, and urticarial vasculitis. There are also specific forms of arteritis, including coronary arteritis, equine viral arteritis, giant cell arteritis (cranial, granulomatous, or temporal arteritis or Horton's disease), infantile arteritis, infectious arteritis, arteritis obli¢terans (endarteritis obliterans), rheumatic arteritis, syphilitic arteritis, Takayasu's arteritis (aortic arch, or brachiocephalic arteritis or Martorell's syndrome or pulseless disease), tuberculous arteritis, endarteritis obliterans, arteritis umbilica¢lis, and verminous mesenteric arteritis.

Cystic fibrosis (CF) is an inherited disease characterized by an abnormality in the glands that produce sweat and mucus. It is chronic, progressive, and is usually fatal. The basis for the problem with CF lies in an abnormal gene, which results in an atypical electrolyte transport system within the cells of the body. The abnormal transport system causes the cells in the respiratory system, especially the lungs, to absorb too much sodium and water. This causes the normal thin secretions in our lungs to become very thick and hard to remove. The high risk of infection in the respiratory system leads to damage in the lungs, lung that do not work properly, and eventually death of the cells in the lungs. The

most common causes for infection in the lungs are Staphylococcus aureus, Haemophilus influenza and Pseudomonas aeruginosa (PA). The disorder itself is largely untreatable.

Osgood-Schlatter disease is a common form of inflammation of the knee in active adolescents. It has no pharmaceutical treatment per se. Other inflammations of the knee include Sinding-Larsen-Johansson disease, Patellofemoral syndrome, and osteochondritis dissecans.

Adhesive capsulitis is a type of inflammation of the shoulder. Its origin is usually unknown.

The above list is by no means complete, but demonstrates the extraordinary breadth of causes, mechanisms and treatment (or lack thereof) for inflammation.

It must be noted that an inflammatory response is a normal body process and for good reason. A certain level of inflammatory response is needed to protect the body from invading organisms, especially bacteria, viruses, and parasites. An acute inflammatory response is needed to activate the healing process for burns, mediated by a range of MMPs. In sprains or other ligament injuries, some inflammatory response is needed initially to initiate repair of the damage. In mechanical wounds, some inflammatory response is required for satisfactory wound healing and indeed anti-inflammatory drugs such as cortisone can impair healing when administered at the time of wounding. In fact, inflammation is too important to be dependent on a single pathway and so inflammation can be initiated by numerous different systems, and generally, if one fails or is thwarted, another can do some or all of the job.

Note that many other disorders have been suggested as being directly related to PDE4, such as non-insulin dependent diabetes, Leishmaniasis, depression and dementia to name just some.

(2) The nature of the invention and predictability in the art: The invention is directed toward the treatment of disease and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(3) Direction or Guidance: That provided is very limited. The dosage information that is provided on page 50 is generic, that is, it is not linked to any specific disease.

(4) State of the Prior Art: The prior art has established that there is no common mechanism by which all, or even most, inflammations arise. Mediators include bradykinin, serotonin, histamine, fibrin, PDE-IV, kallikrein, plasmin, thrombin, PAF, Mac-1, VLA-4, VLA-5, VLA-6, VCAM-1, LFA-1, ICAM-1, Prostaglandins and cyclic endoperoxides (particularly prostacycline, prostaglandin E2, and thromboxane A2), leukotrienes (especially LTB4, LTC4, LTD4, and LTE4) and cytokines, and many, others. Examples of pro-inflammatory cytokines include IL-1I, IL-19, IL-6, IL-8, IL-18, MIP-1a, IFN-K and TNF-I. The Complement Pathway, which exists in two separate branches, uses C1, C4a, C4b, C2, C3a, C3b, C5a, C5b, C6, C7, C8 and C9, as well as the membrane attack complex (MAC) and other complexes, C3 and C5 convertase enzymes, Magnesium ions, and Factors B, D, F, H, etc.

The prior art knows that mediation of inflammation is among the most pervasive and complex of all body process. There are complex interactions among just the cytokines, and just in certain types of inflammatory responses. As a second example, the Hageman factor is a protein that initiates three different processes: a) the intrinsic clotting process which operates via thrombin and fibrin, b) the fibrinolytic system which produces fibrinolysis via plasmin and 3) the kallikrein/kinin cascade, which produces the kinins, e.g. bradykinin. Further, Plasmin can also activate C3 and C5 in the complement cascade (an entirely separate set of vascular events) producing C3a and C5a, respectively, as can thrombin.

Further, the prior art knows that there are many paradoxical features in the inflammation system. As an example, in lung inflammation, nitric oxide appears to be a pro-inflammatory mediator in acute situations e.g. ARDS but anti-inflammatory in more stable situations. As a second example, the cytokine TGF-beta-1 possesses both pro-inflammatory and anti-inflammatory activities. Virtually all cells have TGF-beta-1 receptors, and the cytokine has many other roles other than in inflammation. As a third example, CRF appears to have both pro-inflammatory and anti-inflammatory activities.

Thus, the prior art knows that, treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally.

These compounds are trifluoromethyl purines with a particular substitution pattern in 2 positions. So far as the examiner is aware, no polyfluoro-alkyl purines of any kind are in use for such disorders, or for the treatment of memory impairment.

(5) Working Examples: There are no working examples of treatment of any disorder at all. Indeed, no specific biological data is presented for any specific compound.

(6) Skill of those in the art: For a compound or genus to be effective against inflammation generally is contrary to the present understanding of medical science. It establishes that it is not reasonable for any agent to be able to treat inflammation generally. That is, the skill is so low that no compound effective generally against inflammatory disorders has ever been found. In terms of the individual inflammatory disorders, this is completely varied. It ranges from areas where the skill level is high, as in asthma, to ARDS, where the skill level is so low that there is no effective pharmacological treatment.

The skill level for treating memory impairment in general is very low. There is no such thing as a drug that will treat memory impairment in general. The art knows that memory impairment can arise from a huge number of extremely diverse sources. Memory impairment arises from dementias, such as Alzheimer's disease, Lewy body Dementia, multi-infarct dementia (MID), strategic infarct dementia, LID, ThD, and Binswanger's disease, and Pick's Disease. It can arise from many types of brain tumors. A number of mental disorders, including schizophrenia, bipolar disorder and obsessive-compulsive disorder can cause memory impairment. It can arise from Fibromyalgia, Vitamin B1 deficiency, psychological trauma, complex partial seizures, and Parkinson's Disease. Any number of syndromes, such as Down's syndrome, XXX syndrome, Hurler's syndrome, Kleine-Levin syndrome, Landau-Kleffner syndrome, and Klüver-Bucy Syndrome give rise to memory impairment. Memory impairment can arise from the ingestion of psychotropic drugs, such as alcohol (e.g. alcoholic blackouts), marihuana and glue sniffing. It can arise from toxic neuropathies, radiation injury to the brain, metabolic disorders (e.g.

Mucopolysaccharidosis I) and from some Demyelinating Diseases (notably Multiple Sclerosis). Other common causes include epilepsy, mental retardation, head injury, Meningitis, and atherosclerosis. Because the formation and retrieval of memories is such a complex process, there cannot be a treatment of it in general because so many entirely different things can go wrong. For example, a method which prevents degeneration of long term memory will have no effect on a e.g. anterograde amnesia, since that is a problem which occurs prior to the production of the long-term memory. In fact, memory problems are generally approached by treating the underlying cause. Thus, the memory impairment in Alzheimer's Disease can be treated by treating the Alzheimer's Disease itself. Those arising from schizophrenia, meningitis and atherosclerosis can be approached by medicines for those disorders. Of course, there is no one drug that can treat these generally, since these have different modes of action. However, many, many of these disorders have no pharmaceutical treatment. Mental retardation and Down's syndrome for example are common causes of memory impairment, but there is no treatment for either. Most brain tumors cannot be treated with pharmaceuticals. Many dementias, such as Binswanger's disease, or Pick's Disease, simply do not respond to drugs. And in many cases, e.g. AAMI the true causes are unknown. As a result, large numbers of memory impairments have no pharmaceutical treatments which are accepted as effective. For example, the agnosias and aphasias cannot be treated per se. There is no drug for AAMI or Korsakoff's syndrome or multi-infarct dementia. The notion that a drug effective for Alzheimer's Disease will be effective for other dementias is absolutely false. The Alzheimer's drugs are completely ineffective, for example, in the assorted vascular dementias, in FTDP-17 family and Pick's disease just to name some.

(7) The quantity of experimentation needed: Owing to the factors listed above, especially in points 1, 4 5, and 6, experimentation needed will be extensive. Because of the sheer scope of this claim language, dozens of unrelated diseases will have to be tested. Many of these are already known to be resistant to pharmacological treatment as noted above.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

*Claim Objections*

Claim 74 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 571-272-0663. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on (571)272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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12/15/05